

REMARKS

Claims 82-91 presently appear in this case. No claims have been allowed. The Official Action of November 23, 2010, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for the treatment of an ear disorder in a subject in need of such treatment. The treatment comprises administering into the ear canal of the subject a pharmaceutical agent known to affect an ear disorder, in the form of foam or a mousse. The invention also relates to a dispensing device for dispensing medication to the ear. The dispensing device includes a container containing a medication formulation comprising a medication known to affect an ear disorder, in such a manner that, when the medication formulation is dispensed from the container, it is dispensed in the form of a foam or mousse. The device also includes a pipe that extends from the container and that allows access of the foam or mousse to the ear.

Applicant hereby respectfully requests withdrawal of the finality of the Office Action of November 23, 2010. All of the rejections are new and the Cortifoam[®] reference was newly cited. This new reference and the new rejections were not necessitated by the amendment to the claims by applicant.

All of these rejections would have been equally applicable to the claims as they read prior to the last amendment.

Furthermore, the examiner should have anticipated that applicant would try to antedate references only available under 35 USC 102(a) or 102(e). As stated in MPEP 707.07(a):

A second or any subsequent action on the merits in any application or patent involved in reexamination proceedings should not be made final if it includes a rejection, on prior art not of record, of any claim amended to include limitations which should reasonably have been expected to be claimed.

Accordingly, reconsideration and withdrawal of the finality of the Office Action of November 23, 2010, is respectfully urged.

Claims 84 and 90 have been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the specification does not disclose "a pipe that extends from the container and allows access of the foam or mousse to the ear." The examiner states that applicant has not identified support for the claimed limitation in the specification and the examiner can find none. The examiner states that this is a new matter rejection. This rejection is respectfully traversed.

The specification as filed does not use the term "pipe" but it uses the terms "extension, nozzle or tube"

(see paragraphs [0059], [0109], and [0127] of the published application). The main dictionary definition of "pipe" is "a hollow cylinder or tube used to conduct a liquid, gas, or finely divided solid." Thus, the terms "pipe" and "tube" are substantially synonymous.

Nevertheless, in order to obviate this rejection, the specification has now been amended at paragraph [0109] to read "through an extension, nozzle or tube (such as the pipe shown in Figures 1 and 2), said extension ...". The drawing clearly shows a pipe, which is a form of a tube, and therefore this parenthetical expression in the specification provides no new matter and yet fully supports the language of the present claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 85, 86, 88 and 91 have been rejected under 35 USC 112, second paragraph, as being indefinite. The examiner states that claim 85 recites the limitation "said dispensing device" in line 2, but there is no antecedent basis for this term in the claim or claim 82.

Claim 85 has now been amended to depend from claim 83, thus obviating this part of the rejection.

The examiner states that claims 86 and 88 recite the limitation "the at least one" in line 2, but there is

insufficient antecedent basis for this limitation in the claims or in the claims from which they depend.

Claim 86 and 88 have now been amended to change the term "at least one pharmaceutically active agent" to read "pharmaceutical agent," which finds support in claim 82, from which claims 86 and 88 depend. Accordingly, this part of the rejection has now been obviated.

The examiner states that claim 91 recites the limitation "the dispensing device in accordance with claim 89" but there is insufficient antecedent basis for this limitation in claim 89.

Claim 91 has now been amended to depend from claim 90, thus obviating this part of the rejection.

Accordingly, reconsideration and withdrawal of the entire indefiniteness rejection is respectfully urged.

Claims 90 and 91 have been rejected under 35 USC 102(b) as being anticipated by the Cortifoam[®] reference. The examiner states that Cortifoam[®] is a foam composition comprising hydrocortisone acetate stored in a container of a device that is suitable for administering foam formulations and that the device contains a pipe that extends from the container, noting the diagrams on page 10. The examiner considers that the claim language "for dispensing medication to the ear" is an intended use limitation which cannot

distinguish over the prior art as long as the prior art structure is capable of performing the intended use. This rejection is respectfully traversed.

Cortifoam[®] is a foam composition comprising hydrocortisone acetate indicated as adjunctive therapy for treating ulcerative proctitis. Indeed, Cortifoam[®] is stored in a container. However, as explicitly described for Cortifoam[®] in Drugs.com, the device includes a container and an applicator that are two separate components (p. 8, under Directions for Use, and p. 9 of the drug information by Drugs.com). The manufacturer provides clear directions NOT to insert any part of the aerosol container directly into the anus (p. 8 of Cortifoam[®] information by Drugs.com; and Cortifoam[®], Physicians' Desk Reference). Only the separate applicator is applied to the anus (p. 8 of Cortifoam[®] information by Drugs.com). As specified under Directions for Use of Cortifoam[®] and as seen from the illustrations on the box, the applicator is filled with the foam composition stored in the container by placing the tip of the applicator onto the nose of the container cap and then pressing the cap flanges so as to fill the applicator with the foam. When the foam reaches the fill line of the applicator, the applicator is removed from the container cap. The tip of the applicator is then inserted into the anus. Thus, according to both

references, none of the container parts, and specifically the container cap, is inserted into the anus.

In contrast, the device of the present invention comprises a container containing the medication and a pipe that extends from the container (see Figs. 1 and 2 of the present specification). The pipe allows access of the foam to the ear. There is no separate applicator to be filled with the foam medication and to be applied to the ear. The pipe of the present device is intended to be applied to the ear.

The Cortifoam[®] container contains no pipe whatsoever. Even when the applicator is attached to the container for filling of the applicator, the applicator cannot be considered to be "a pipe that extends from the container and that allows access of the foam or mousse to the ear" because there is no outlet from the applicator when it is attached to the container. The applicator of Cortifoam[®], when attached to the container, cannot allow access of the foam to anything as it has no outlet. The only outlet is stuck into the container. Thus, claims 90 and 91 recite a dispensing device which is distinct and different from the device used for Cortifoam[®] administration. The device used for Cortifoam[®] administration does not have the claimed pipe and cannot perform the claimed intended use (even if one ignores the specific ingredient being dispensed and the intended delivery site recited in the

claim). Therefore, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 82-91 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Purwar in view of Cortifoam®. The examiner alleges that Purwar teaches a method of treating otitis by introducing an antibacterially-effective amount of a composition comprising a non-toxic, topical, otic pharmaceutical composition comprising ciprofloxacin, a non-ionic viscosity augments, preservative, water, hydrocortisone, lecithin, and polysorbate 20-80. The examiner further alleges that Cortifoam® is a foam composition comprising hydrocortisone acetate stored in a container of a device that is suitable for administering foam formulations and which contains a pipe that extends from the container. The examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Purwar and Cortifoam® with a reasonable expectation of successfully preparing a foam formulation for the easy delivery of an active agent topically to the desired site. The examiner further alleges that it has been held that "when an application simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." The

examiner further alleges that "[W]hen the question is whether a patent application claiming the combination of elements of prior art is obvious, the relevant question is whether the improvement is more than the predictable use of prior art elements according to their established functions." This rejection is respectfully traversed.

Applicant wishes to note that ear drops for treating ear disorders have been known for about a hundred years. Foams, in general, for delivery of therapeutic agents to a patient have been known for about fifty years. The present application refers to the known art in the background of the invention (see paragraphs [0010] to [0027] of US 2008/0075670). However, a method for treating ear disorders comprising administering into the ear canal a pharmaceutical agent in the form of a foam or mousse has not been taught or used prior to the filing of the present application.

Moreover, the present application clearly and explicitly discloses that use of a foam composition for treating ear disorders provides advantages far beyond the established functions of ear drops known in the art (see the abstract and paragraphs [0032], [0079] and [0080] of the published application, as well as page 13, last paragraph, through p. 15, second paragraph, of the Amendment filed on September 20, 2010, in connection with this application). It

should be noted that the ear canal does not belong to body cavities that include mucous membranes, such as the vaginal, anal or nasal cavities, as the ear does not contain any mucous membrane. The surface of the ear canal is covered by unique skin which has the characteristic feature of secreting cerumen.

With respect to the Cortifoam[®] reference, Cortifoam[®] is a foam composition comprising hydrocortisone acetate indicated as adjunctive therapy for treating ulcerative proctitis in patients who cannot retain hydrocortisone or other corticosteroid enemas (p. 2 of the drug information by Drugs.com). Thus, Cortifoam[®] is administered to the anus. Purwar discloses a method of treating otitis which comprises introducing a composition comprising an otic pharmaceutical composition comprising ciprofloxacin in aqueous solution, a non-ionic viscosity augments, a preservative, water sufficient to produce aqueous composition, hydrocortisone, lecithin and polysorbate 20 to 80. Neither of the references, alone or in combination, discloses or suggests use of a foam composition for treating ear disorders.

Even if one combines Purwar and Cortifoam[®], since the ear canal and rectum are structurally distinct, there was no suggestion that a foam composition introduced into the ear would enable retention of the pharmaceutical agent.

Certainly, one would not expect that a pharmaceutical composition in the form of a foam or mousse, when administered into the ear canal, would release the active substance slowly and thus would enable infrequent applications of the composition and hence improved compliancy, would evaporate spontaneously, and would provide prolonged contact of the pharmaceutical agent with the ear canal so as to enhance treatment effectiveness, all of which are disclosed for the method of the present invention (see, for example, abstract and paragraphs [0032], [0079], and [0080] of the present application). Thus, not only has the method and device recited in claims 82-91 not been taught or suggested by Purwar in view of Cortifoam[®], they also provide significant improvement, which is clearly more than the predictable use of the method disclosed by Purwar and the foam composition Cortifoam[®].

In order to quantify the unexpected improvement that one obtains when administering the medicament to the ear by foam as opposed to by ear drops, certain experiments have been conducted. The examiner's attention is respectfully invited to the declaration of Dr. Rodrigo Yelin, submitted herewith. Dr. Yelin was the Study Director with respect to certain clinical trials that were conducted relating to the method of administration of the present invention. It can be seen from

this declaration that Study #1 was a clinical study for assessing safety, efficacy and clinical equivalence of an otic foam formulation of ciprofloxacin in comparison to commercial ciprofloxacin ear drops (Ciloxan of Alcon Labs) in the treatment of diffuse otitis externa (swimmer's ear). This study and the results thereof are described in detail in Marom et al., "Comparison of safety and efficacy of foam-based versus solution-based ciprofloxacin for acute otitis externa," *Otolaryngology-Head and Neck Surgery*, 143:492-499 (2010) (hereinafter Marom), which is being submitted on even date herewith. It can be seen from Table 2 of Marom that 100% of all patients receiving either the foam or the drops reached a positive outcome as determined by resolution or improvement on the third visit. The paragraph bridging pages 495-496 indicates that with the entire intent-to-treat (ITT) population, the percentage of patients with a positive outcome in both treatment groups was also very high and similar (93.8% for the foam-based ciprofloxacin group vs. 93.6% for the solution based ciprofloxacin group).

Moreover, the foam formulation was found to be more advantageous than the Ciloxan ear drops in the fraction of patients showing complete resolution of signs and symptoms of the disease (Table 2 of Morom - 86.2% for foam formulation vs. 78.6% for solution-based formulation). Additionally, the last

paragraph on page 496 reports that otic discharge (otorrhea) completely ceased in the foam-based ciprofloxacin group (100%) but was not completely resolved in the solution-based ciprofloxacin group (84.6%) after the completion of the therapeutic course.

Study #1 was primarily concerned with safety and efficacy. Following Study #1, Study #2 was conducted, which proves the unexpected clinical superiority of the foam-based formulation of the present invention. The objective of the second study was to assess whether a single daily application of the foam formulation provides equivalent therapeutic effect in the treatment of acute diffuse otitis externa as compared to the approved dose of Ciloxin ear drops (applied twice a day). The results establish, as seen in Table 1 of the declaration, that only 7 doses of foam formulation are sufficient to cure otitis externa while 14 doses are required when using ear drops containing the same antibiotic at the same level. This establishes, therefore, that the foam formulation presents a major advantage to the user in terms of efficacy and safety as it requires only half of the amount of antibiotic to obtain the desired therapeutic effect while reducing two-fold the potential side effects of the antibiotic.

Purwar administers by instillation, meaning ear drops. The rejection is based on the examiner's assumption that administering by foam would provide equivalent results to administering by ear drops. However, even if the examiner has established a *prima facie* case of obviousness, despite the reasoning providing hereinabove, the evidence of unexpected results proved herein rebuts such a *prima facie* case of obviousness and establishes the unexpected superiority of foam administration versus the drop by drop instillation technique of Purwar. Accordingly, for these reasons as well, reconsideration and withdrawal of this rejection are respectfully urged.

Furthermore, claims 90 and 91 cannot be made obvious by any combination of Purwar and Cortifoam[®] as neither reference discloses a container with a pipe. Thus, Purwar fulfills none of the deficiencies of Cortifoam[®] as discussed above with respect to the anticipation rejection. Reconsideration and withdrawal of this rejection for claims 90 and 91 are further and specifically respectfully urged.

Claims 82-91 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Purwar in view of Abram. The examiner alleges that Purwar teaches a method of treating otitis by introducing an antibacterially-effective amount of a composition comprising a non-toxic, topical, otic

pharmaceutical composition comprising ciprofloxacin, a non-ionic viscosity augmenter, preservative, water, hydrocortisone, lecithin, and a polysorbate 20-80. The examiner further alleges that Abram teaches a pharmaceutical aerosol foam composition including a pharmaceutically active ingredient, an occlusive agent, an aqueous solvent, and an organic cosolvent, the pharmaceutically active ingredient being insoluble in both water and occlusive agent. The examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Purwar and Abram with a reasonable expectation of successfully preparing a foam formulation for the easy delivery of an active agent topically. This rejection is respectfully traversed.

Abram does not remedy the deficiencies of Purwar and this combination of references does not make the present invention obvious for the same reasons as discussed above with respect to the Purwar/Cortifoam[®] combination. Abram discloses a pharmaceutical aerosol foam composition including a pharmaceutically active ingredient, an occlusive agent, an aqueous solvent, and an organic cosolvent, the pharmaceutically active agent being insoluble in both water and the occlusive agent (see, col. 1, lines 48-57, of Abram). According to Abram, the mousse formulation which includes a

relatively low amount of an occlusive agent "is able to reduce trans epidermal water loss and hence in theory to increase skin permeability to effect greater drug skin penetration" (see col. 1, lines 60-64 of Abram). Thus, the foam formulation disclosed by Abram is aimed at increasing drug penetration through the skin. Even if one combines Purwar and Abram, he or she would not obtain the method and device of the present invention nor expect obtaining the advantages associated therewith. There would be no motivation for one of ordinary skill in the art of treating ear diseases to use a formulation created for the purpose of transepidermal administration.

Moreover, the method of the present invention provides unpredicted advantages over Purwar in view of Abram for the same reasons as discussed above with respect to Cortifoam[®]. As indicated above, the method for the treatment of an ear disorder according to the present invention enables, for example, releasing the active agent slowly so as to enable non-frequent applications of the composition into the ear and thus improve compliancy, enables prolonged and increased contact of the active agent with the ear canal skin and thus facilitates healing, eliminates the need to tilt the head or to use ear wicks, provides uniform concentration of the active agent so to increase treatment effectiveness, and provides

metered or measured dosing of the composition (see abstract and paragraphs [0032], [0079], and [0080] of the published application). None of these advantages are suggested by Abram.

Furthermore, the declaration proves that the foam-based formulation application method of the present invention is unexpectedly superior in efficacy as compared to the eardrops of Purwar. The same amount of active ingredient per dose in the foam formulation cured the condition with half the number of applications as the ear drop formulation. This unexpected improvement proves the unobviousness of the present invention over any combination of Purwar and Abram.

Thus, not only have the method and device recited in claims 82-91 not been taught or suggested by Purwar in view of Abram, they provide significant improvement, which is clearly more than the predictable use of the method disclosed by Purwar and the foam disclosed by Abram. Accordingly, claims 82-91 are patentable over Purwar in view of Abram. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 82-91 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Klein in view of Purwar. The examiner alleges that Klein teaches topical or local application comprising at least one corticosteroid, from

about 1 to 4% by weight of solubilization agents consisting essentially of a combination of at least one glyceryl ester of a fatty acid of 6 to 22 carbon atoms and a betaine surfactant, from about 10% to 50% by weight of the composition of an alkanol cosolvent, and from about 20% to 50% water. The examiner further alleges that local application as disclosed by Klein means use in body cavities such as vaginal, nasal, etc. The examiner asserts that Klein discloses a new topical or local preparation which can produce a foam when packaged either in the form of an aerosol or a non-aerosol foam-forming closure system. The examiner alleges that Klein lacks disclosure of a method of treating ear disorders and a device comprising a container and a pipe, which deficiency is allegedly cured by Purwar. The examiner further alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klein and Purwar with a reasonable expectation of successfully preparing a foam formulation for the easy delivery of an active agent topically. This rejection is respectfully traversed.

Klein discloses a composition for topical or local application in body cavities including mucous membranes, i.e., vaginal, nasal, anal, etc. As mentioned above, the ear canal does not belong to body cavities which include mucous

membranes, such as the vaginal, anal or nasal cavities, as the ear does not contain any mucous membrane. The surface of the ear canal is covered by unique skin which has the characteristic feature of secreting cerumen. The composition of Klein comprises an essentially water-washable base which provides an occlusive film for longer and better therapeutic activity. Klein further discloses that the composition releases the medicament more quickly and effectively, and spreads evenly (see col. 1, lines 48-50 and lines 58-65 of Klein).

Purwar does not provide motivation to use the foam of Klein in the ear. Even if Klein and Purwar are combined, one would not obtain the method and device of the present invention nor expect obtaining the advantages associated therewith, all as detailed above. Furthermore, Purwar does not teach a container with a pipe, as alleged by the examiner. Accordingly, for all of the reasons discussed in the response to the other obviousness rejections, including the evidence of unexpected results over the ear drop formulation, such as that disclosed by Purwar, and for the additional reasons presented herein, reconsideration and withdrawal of this rejection are also respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and

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fully comply with 35 USC 112. Reconsideration and allowance
are therefore earnestly solicited.

Respectfully submitted,

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